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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NUCLEIC ACID LIGANDS AND USES THEREFOR

(57) Abstract: The present invention relates to novel nucleic acid molecules or ligands or aptamers with affinities for specific target molecules, and uses of such molecules. The target molecules are fibrillar proteins in all forms of the protein that is to say its monomeric, pre-fibrillar, protofibrillar and mature fibrillar forms. The molecules of the present invention are therefore useful as diagnostic or therapeutic or screening agents, or as potential lead compounds for rationalised drug design.

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INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 03/04798

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YLERA FRANCISCO ET AL: "Selection of RNA aptamers to the Alzheimer's disease amyloid peptide" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 290, no. 5, 8 February 2002 (2002-02-08), pages 1583-1588, XP002286523 ISSN: 0006-291X the whole document	1-6, 8-10, 12-17, 20-34
X	DE 199 16 417 A (SCHERING AG) 19 October 2000 (2000-10-19) page 3, line 50 - line 67; claims 2,10-12	1-6, 8-10, 12-17, 20-34

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2004	21. 10. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Costa Roldán, N

Form PCT/ISA/210 (second sheet) (January 2004)

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 756 291 A (GRIFFIN LINDA ET AL) 26 May 1998 (1998-05-26) abstract	1-6, 8-10, 12-17, 20-34
A	WO 01/88123 A (ISIS INNOVATION ;JAMES WILLIAM SIWARD (GB)) 22 November 2001 (2001-11-22) page 7 - page 8; table 1	
T	IVANOVA MAGDALENA I ET AL: "Role of the C-terminal 28 residues of beta2-microglobulin in amyloid fibril formation." BIOCHEMISTRY, vol. 42, no. 46, 25 November 2003 (2003-11-25), pages 13536-13540, XP002286524 ISSN: 0006-2960 (ISSN print) the whole document	1-6, 12-17, 20-34

INTERNATIONAL SEARCH REPORT

ıational application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 18,19
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-6,8-10,12-17,20-34

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 18,19

Present claims 18 and 19 relate to products (to nucleic acid ligands) defined only by reference to a desirable characteristic or property, namely that said nucleic acid ligands are capable of binding the amyloid fibril protein. However, this sole feature does not allow the skilled person to understand which structural features characterize the compounds. Said claims therefore lack clarity (Article 6 PCT) to the extent that a meaningful search over the whole of the claimed scope is impossible.

Claimd 18 and 19 are clear only insofar as they relate to specific nucleic acid ligands referred to in the description that have said property. As such subject-matter is covered by the other claims, claims 18 and 19 have not been search as such.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1 (claims 1-6, 12-15, 20-34, all partially).

A purified and isolated non-naturally occurring RNA ligand (labelled or unlabelled) to A-Beta-40 monomeric target protein consisting of the nucleic acid sequence with SEQ ID NO: 1, a vector comprising said RNA ligand, a host cell comprising said vector, a pharmaceutical composition comprising said RNA ligand, the use of said RNA ligand for manufacture of a medicament, and a method for the isolation of said RNA ligand.

Inventions: 2 to 16 (claims 1-6, 12-15, 20-34, all partially)

Inventions 2 to 16, as invention 1 wherein the nucleic acid sequence molecule consists of SEQ ID NOS: 2 to 16, respectively.

Invention 17 (claims 1-4, 5, 7, 19-34 all partially).

A purified and isolated non-naturally occurring RNA ligand to A-Beta-40 prefibrillar target consisting of the nucleic acid sequence with SEQ ID NO: 17, a vector comprising said RNA ligand, a host cell comprising said vector, a pharmaceutical composition comprising said RNA ligand, and a method for the isolation of said RNA ligand and a method for the isolation of said RNA ligand.

Inventions: 18 to 36 (claims 1-4, 5, 7, 19-34, all partially)

Inventions 18 to 36, as invention 17 wherein the nucleic acid sequence molecule consists of SEQ ID NO: 18 to 36, respectively.

Invention 37 (claims 1-5, 8, 12-15, 19-34, all partially)

A purified and isolated non-naturally occurring RNA ligand to A-Beta-40 protofibrillar target consisting of the nucleic acid sequence with SEQ ID NO: 37, a vector comprising said RNA ligand, a host cell comprising said vector, a pharmaceutical composition comprising said RNA ligand, and a method for the isolation of said RNA ligand and a method for the isolation of said RNA ligand.

Inventions: 38 to 55 (claims 1-5, 8, 12-15, 19-34, all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Inventions 38 to 55, as invention 37 wherein the nucleic acid sequence molecule consists of SEQ ID NO: 38 to 55, respectively.

Invention 56 (claims 1-5, 9, 12-18, 20-34, all partially)

A purified and isolated non-naturally occurring RNA ligand to native human Beta-2 microglobulin consisting of the nucleic acid sequence with SEQ ID NO: 58, a vector comprising said RNA ligand, a host cell comprising said vector, a pharmaceutical composition comprising said RNA ligand, and a method for the isolation of said RNA ligand and a method for the isolation of said RNA ligand.

Inventions: 57 to 69 (claims 1-5, 9, 12-18, 20-34, all partially)

Inventions 57 to 69, as invention 56 wherein the nucleic acid sequence consists of SEQ ID NO: 59 to 71, respectively.

Invention 70 (claims 1-5, 10, 12-18, 20-34, all partially)

A purified and isolated non-naturally occurring RNA ligand to immature human fibril Beta-2 microglobulin consisting of the nucleic acid sequence with SEQ ID NO: 72, a vector comprising said RNA ligand, a host cell comprising said vector, a pharmaceutical composition comprising said RNA ligand, and a method for the isolation of said RNA ligand and a method for the isolation of said RNA ligand.

Inventions: 71 to 88 (claims 1-5, 10, 12-18, 20-34, all partially)

Inventions 71 to 88, as invention 70 wherein the nucleic acid sequence molecule binds to Beta-2-microglobulin immature fibril protein target and consists of SEQ ID NO: 73 to 90, respectively.

Invention 89 (claims 1-5, 11, 12-18, 20-34, all partially)

A purified and isolated non-naturally occurring RNA ligand to mature human fibril Beta-2 microglobulin consisting of the nucleic acid sequence with SEQ ID NO: 91, a vector comprising said RNA ligand, a host cell comprising said vector, a pharmaceutical composition comprising said RNA ligand, and a method for the isolation of said RNA ligand and a method for the isolation of said RNA ligand.

Inventions: 90 to 103 (claims 1-5, 11, 12-18, 20-34, all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Inventions 90 to 103, as invention 89 wherein the nucleic acid sequence molecule binds to Beta-2-microglobulin immature fibril protein target and consists of SEQ ID NO: 92 to 105, respectively.

Invention 104 (claims 16-18, all partially)

The peptide sequence consisting of SEQ ID NO: 111 as a target for selecting nucleic acid ligands (RNA aptamers) and that retain the ability to form amyloid fibrills, the use of said peptide sequence, and a purified and isolated nucleic acid ligand to a fibrillar protein wherein the target comprises the binding motif of SEQ ID NO: 111.

Inventions: 105 and 106 (claims 16-18, all partially)

Inventions 105 and 106, as invention 104 wherein the target sequence consists of SEQ ID NO: 112 and 113, respectively.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ›nal Application No
PCT/GB 03/04798

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19916417 A	19-10-2000	DE 19916417 A1	19-10-2000
US 5756291 A	26-05-1998	NONE	
WO 0188123 A	22-11-2001	AU 5856801 A	26-11-2001
		CA 2410028 A1	22-11-2001
		EP 1287126 A1	05-03-2003
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		US 2003162225 A1	28-08-2003